

Viekira Pak (Ombitasvir, Paritaprevir, and Ritonavir Tablets; Dasabuvir Tablets): All-Oral Fixed Combination Approved for Genotype 1 Chronic Hepatitis C Infection

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Approximately 130 million to 170 million individuals worldwide, including 3.2 million Americans, are infected with chronic hepatitis C virus (HCV), making it the most common blood-borne disease.^{1,2} Chronic HCV infection is a silent epidemic; the disease can remain quiescent for decades before clinically significant symptoms appear.³

The prevalence of HCV and its complications are expected to rise as Americans who are currently living with HCV enter their 50s and 60s.⁴ Research indicates that by 2015, more than 3 million individuals will have HCV infection that has been present for 20 years or more, which will result in a significant increase in the incidence of advanced liver disease, including cirrhosis, decompensated cirrhosis, and liver cancer.^{5,6} The Centers for Disease Control and Prevention estimates that for every 100 individuals infected with HCV, 1 to 5 will die from liver cancer or cirrhosis.¹

In addition to causing substantial morbidity and mortality, HCV is associated with significant financial consequences.^{3,7} A 2000 study estimated that between 2010 and 2019, the direct medical expenditures for HCV-related conditions will reach nearly \$11 billion, the cost of morbidity from disability related to decompensated cirrhosis and hepatocellular carcinoma would reach approximately \$21 billion, and the societal cost of premature mortality for patients aged <65 years will exceed \$54 billion (in 1999 US dollars).⁷

HCV is currently the only chronic viral infection that is curable with antiviral therapy. The goals of current anti-HCV approaches are to eradicate infection, to avoid complications, and to prevent the spread of HCV to others.⁸

In the early 1990s, single-agent interferon was the standard of care for patients with HCV infection. Single-agent interferon represented a significant therapeutic advancement, because until then there was no treatment available for HCV infection; however, single-agent interferon offered a sustained virologic response (SVR) rate of less than 10% in patients with HCV genotype 1, the most common HCV subtype.⁸ Interferon was then

used in combination with ribavirin, increasing the SVR rate by another 14% to 22%.⁸ In the early 2000s, once-weekly pegylated forms of interferon were introduced. The combination of pegylated interferon with ribavirin increased SVR rates to more than 50% in patients with HCV genotype 1. However, HCV genotype 1 was less responsive than HCV genotype 2 or 3.^{9,10} Because of this variability in HCV response, low response rates in common HCV subpopulations (ie, black patients, patients with cirrhosis), and side effects associated with interferon and ribavirin, there remained a need to develop novel antiviral therapies.⁸

The treatment options for patients with HCV have evolved significantly in the past several years. In 2011, 2 first-generation protease inhibitors, telaprevir and boceprevir (also known as direct-acting antiviral drugs), were approved by the US Food and Drug Administration (FDA).^{11,12} Both agents offered significant efficacy in patients with HCV genotype 1 infection as measured by SVR rates.^{11,12}

In December 2013, the FDA approved sofosbuvir (Sovaldi) in combination with ribavirin—the first interferon-free, all-oral regimen—for the treatment of patients with HCV genotype 2 or 3.^{13,14} In addition, sofosbuvir in combination with interferon and ribavirin is approved for the treatment of patients with HCV genotype 1 and genotype 4.^{13,14} Candidates for sofosbuvir therapy include patients with hepatocellular carcinoma who meet Milan criteria (ie, awaiting liver transplantation) and patients with HCV/HIV-1 coinfection.^{13,14} Sofosbuvir regimens require less treatment time than older combination regimens—12 weeks for patients with HCV genotype 1, 2, or 4; and 24 weeks for patients with HCV genotype 3.¹⁴

In October 2014, the FDA approved the fixed-dose combination capsule of ledipasvir and sofosbuvir (Harvoni) for the treatment of patients with HCV genotype 1 infection.¹⁵ This once-daily combination tablet was the first regimen approved for HCV genotype 1 without interferon or ribavirin.¹⁵

Interest in novel therapies for HCV remain strong in

light of the increasing incidence of HCV (and its costly complications), unmet patient needs, and the identification of new drug targets.¹⁶ Efforts continue, with the goals of improving the pharmacokinetics and the tolerability of these agents, as well as determining treatment strategies—interferon-containing and interferon-free (all oral) regimens—that optimize outcomes.¹⁷

Novel Oral Regimen Approved for Genotype 1 Chronic HCV Infection

On December 19, 2014, the FDA approved the combination of ombitasvir, paritaprevir, and ritonavir tablets copackaged with dasabuvir tablets (Viekira Pak; AbbVie) for use with or without ribavirin for the treatment of patients with genotype 1 chronic HCV infection, including patients with compensated cirrhosis.¹⁸ This combination includes 3 new drugs (ombitasvir, paritaprevir, and dasabuvir) and an older drug (ritonavir) that are copackaged for oral use; ombitasvir is an HCV NS5A inhibitor; paritaprevir, an HCV NS3/4A protease inhibitor; ritonavir, a cytochrome (CY) P3A inhibitor; and dasabuvir, an HCV nonnucleoside NS5B polymerase inhibitor. Overall, 3 of these medications target HCV at multiple steps in the viral lifecycle.¹⁹

Ombitasvir, paritaprevir, and ritonavir plus dasabuvir combination is the eleventh new drug with breakthrough therapy designation to receive FDA approval.¹⁸ This new regimen was reviewed under the FDA's priority review program, which expedites the assessment of medications for serious conditions that offer a significant improvement in the safety or efficacy.¹⁸

"The new generation of therapeutics for hepatitis C virus is changing the treatment paradigm for Americans living with the disease," said Edward Cox, MD, MPH, Director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research. "We continue to see the development of new all-oral treatments with very high virologic response rates and improved safety profiles compared to some of the older interferon-based drug regimens."¹⁸

Mechanism of Action

The 3 direct-acting HCV antiviral agents—ombitasvir, paritaprevir, and dasabuvir—have distinct mechanisms of action and nonoverlapping resistance profiles.¹⁹ This combination is designed to target multiple steps in the HCV lifecycle. The fourth drug, ritonavir, is not active against HCV; it is a potent CYP3A inhibitor that enhances plasma drug concentrations of paritaprevir and overall drug exposure.¹⁹

Dosing and Administration

The drug includes fixed-dose combination tablets of

ombitasvir (12.5 mg), paritaprevir (75 mg), and ritonavir (50 mg) copackaged with dasabuvir (250 mg).¹⁹ The recommended oral dosage of the combination drug is 2 ombitasvir, paritaprevir, and ritonavir tablets once daily in the morning, and 1 dasabuvir tablet twice daily (ie, morning and evening). The drug should be taken with a meal without regard to fat or caloric content.¹⁹

Table 1 summarizes the recommended treatment regimens and duration of therapy for specific subsets of patients with HCV genotype 1 infection.¹⁹

Clinical Trials

The efficacy and safety of the new 4-drug oral combination were evaluated in 6 randomized, multicenter, clinical trials (**Table 2**).¹⁹⁻²³ A total of 2308 patients with genotype 1 chronic HCV infection received the drug, including patients with cirrhosis or with mild hepatic impairment (ie, Child-Pugh A).¹⁹

In the 6 clinical trials, the ombitasvir, paritaprevir, and ritonavir dose was 25/150/100 mg once daily, and the dasabuvir dose was 250 mg twice daily; the dose was not adjusted. For patients who received ribavirin, the ribavirin dose was 1000 or 1200 mg daily, based on the patient's weight (<75 kg or ≥75 kg, respectively).¹⁹

Chronic HCV Genotype 1a Infection without Cirrhosis

Patients with HCV genotype 1a infection without

Table 1 Treatment Regimen and Duration in Patients with Genotype 1 HCV Infection

Patient population	Recommended regimen ^a	Recommended treatment duration
Genotype 1a, no cirrhosis	Ombitasvir, paritaprevir, ritonavir, plus dasabuvir, with ribavirin	12 wks
Genotype 1a, cirrhosis	Ombitasvir, paritaprevir, ritonavir, plus dasabuvir, with ribavirin	24 wks ^b
Genotype 1b, no cirrhosis	Ombitasvir, paritaprevir, ritonavir, plus dasabuvir	12 wks
Genotype 1b, cirrhosis	Ombitasvir, paritaprevir, ritonavir, plus dasabuvir, with ribavirin	12 wks

^aFollow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

^bA 12-week treatment may be considered for some patients based on their treatment history.

HCV indicates hepatitis C virus.

Source: Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), copackaged, prescribing information; February 2015.

Table 2 Randomized, Multicenter Trials with Ombitasvir, Paritaprevir, Ritonavir, plus Dasabuvir, with/without Ribavirin in Patients with Genotype 1 Chronic HCV Infection			
Clinical trial	Trial design	Patient cohort	Ombitasvir, paritaprevir, ritonavir, plus dasabuvir, with/without ribavirin (sample size)
SAPPHIRE-I	Double-blind, placebo-controlled	Without cirrhosis, treatment-naïve, ^a genotype 1a and 1b	With ribavirin (N = 473) Placebo (N = 158)
SAPPHIRE-II	Double-blind, placebo-controlled	Without cirrhosis, treatment-experienced, ^b genotype 1a and 1b	With ribavirin (N = 297) Placebo (N = 97)
PEARL-II	Open-label	Without cirrhosis, treatment-experienced, genotype 1b	With ribavirin (N = 88) Without ribavirin (N = 91)
PEARL-III	Double-blind	Without cirrhosis, treatment-naïve, genotype 1b	With ribavirin (N = 210) Without ribavirin (N = 209)
PEARL-IV	Double-blind	Without cirrhosis, treatment-naïve, genotype 1a	With ribavirin (N = 100) Without ribavirin (N = 205)
TURQUOISE-II	Open-label	With cirrhosis, treatment-naïve and treatment-experienced, genotype 1a and 1b	With ribavirin for 12 wks (N = 208) With ribavirin for 24 wks (N = 172)

^aTreatment-naïve was defined as receiving no previous therapy for HCV infection.
^bTreatment-experienced was defined as patients whose disease previously relapsed, previous partial responders, or previous null responders to pegylated interferon plus ribavirin treatment.
HCV indicates hepatitis C virus.
Source: Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), copackaged, prescribing information; February 2015.

cirrhosis received ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with ribavirin, for 12 weeks in 3 studies: SAPPHIRE-I, SAPPHIRE-II, and PEARL-IV.^{19,21-23} The patients' median age was 53 years (range, 18-70 years).¹⁹ The majority of patients were male (63%) and white (90%), with baseline HCV RNA levels $\geq 800,000$ IU/mL (85%). In these studies, 7% of patients were black or African American, 8% were Hispanic or Latino, and 19% had a body mass index (BMI) ≥ 30 kg/m².¹⁹

Table 3 presents the SVR outcomes for treatment-naïve and treatment-experienced patients who received ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with ribavirin, for 12 weeks in these clinical trials.

Chronic HCV Genotype 1b Infection without Cirrhosis

Patients with HCV genotype 1b infection without cirrhosis received ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with or without ribavirin, for 12 weeks in 2 studies: PEARL-II and PEARL-III.¹⁹ The patients' median age was 52 years (range, 22-70 years). The majority of patients were female (53%) and white (93%), with baseline HCV RNA levels $\geq 800,000$ IU/mL (77%).¹⁹ Overall, 5% of patients were black or African American, and 2% were Hispanic or Latino. In addition, 21% of patients had a BMI ≥ 30 kg/m².¹⁹

Table 4 summarizes the SVR outcomes for the treatment-naïve and treatment-experienced patients who

received ombitasvir, paritaprevir, and ritonavir plus dasabuvir for 12 weeks in these clinical trials.

Chronic HCV Genotype 1a or 1b Infection with Compensated Cirrhosis

A total of 380 treatment-naïve or treatment-experienced patients with HCV genotype 1a or genotype 1b, with cirrhosis, and with mild hepatic impairment (Child-Pugh A) enrolled in TURQUOISE-II, an open-label randomized clinical trial.^{19,20} This clinical trial compared the SVR rates after treatment with ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with ribavirin, for 12 or 24 weeks in patients who were treatment-naïve or who did not reach SVR with previous pegylated interferon therapy.¹⁹

The patients' median age was 58 years (range, 21-71 years).¹⁹ The majority of patients were male (70%) and white (95%), with baseline HCV RNA levels $\geq 800,000$ IU/mL (86%). Overall, 3% of patients were black or African American, 12% were Hispanic or Latino, and 28% had a BMI ≥ 30 kg/m².¹⁹

Treatment outcomes for treatment-naïve and treatment-experienced patients with cirrhosis who received ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with ribavirin, for 12 or 24 weeks are summarized in Table 5.

Durability of Response

In an open-label clinical trial, 92% of patients (526 of 571) who received various combinations of the direct-

acting antiviral agents that are included in the ombitasvir, paritaprevir, and ritonavir plus dasabuvir combination, with or without ribavirin, reached an SVR after 12 weeks of treatment (ie, SVR12).¹⁹ Among patients who reached SVR12, 99% maintained their response through 48 weeks posttreatment.¹⁹

Safety

The pooled data from more than 2000 patients with chronic HCV infection who participated in 6 phase 3 clinical trials were used for the safety assessment of ombitasvir, paritaprevir, and ritonavir plus dasabuvir.¹⁹ These studies evaluated the combination tablets given for 12 or 24 weeks (with or without ribavirin).¹⁹

The safety of ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with ribavirin, was assessed in 770 patients with chronic HCV infection in 2 placebo-controlled clinical trials known as SAPPHERE-I and -II.¹⁹ Adverse events that occurred more frequently in patients who received the 4-drug combination plus ribavirin compared with placebo included fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. Overall, 2% of patients in SAPPHERE-I and SAPPHERE-II experienced a serious adverse event, and less than 1% of patients permanently discontinued treatment as a result of adverse events.¹⁹

The safety of ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with and without ribavirin, was assessed in 401 patients and in 509 patients with chronic HCV infection, respectively, in 3 clinical trials known as PEARL-II, PEARL-III, and PEARL-IV.¹⁹ Adverse events that occurred more frequently in patients who received ombitasvir, paritaprevir, and ritonavir plus dasabuvir with ribavirin compared with the 4-drug combination without ribavirin were pruritus, nausea, insomnia, and asthenia.¹⁹ The majority of adverse events were mild to moderate. Less than 1% of patients permanently discontinued treatment because of adverse events after receiving the 4-drug combination, with or without ribavirin.¹⁹

The safety of the 4-drug combination plus ribavirin was assessed in 380 patients with compensated cirrhosis who received treatment for 12 or 24 weeks in TURQUOISE-II.¹⁹ The type and the severity of adverse events in these patients were comparable to those in patients without cirrhosis who participated in other phase 3 clinical trials. Fatigue, skin reactions, and dyspnea occurred at least 5% more frequently in patients who received ombitasvir, paritaprevir, and ritonavir plus dasabuvir with ribavirin for 24 weeks.¹⁹ The majority of adverse events occurred during the first 12 weeks of dosing in the 12-week and 24-week treatment arms, and were mild to moderate.¹⁹ Serious adverse events were reported by 6% and 5% of patients who received treat-

ment with the new combination plus ribavirin for 12 and 24 weeks, respectively.¹⁹ In each study arm, 2% of patients permanently discontinued the new regimen plus ribavirin as a result of adverse events.¹⁹

Drug Interactions

The concomitant use of ombitasvir, paritaprevir, and ritonavir plus dasabuvir and certain other drugs can result in known and potentially significant drug interactions.¹⁹ Drug interactions may lead to the loss of therapeutic effect of the new regimen, the development of resistance, and clinically significant adverse events from greater exposure to concomitant drugs or to components of ombitasvir, paritaprevir, and ritonavir plus dasabuvir.¹⁹

Contraindications

If the combination pack of ombitasvir, paritaprevir, and ritonavir tablets plus dasabuvir tablets is administered with ribavirin, the contraindications to ribavirin also apply.¹⁹

Because of the risk for toxicity, the ombitasvir, paritaprevir, and ritonavir plus dasabuvir regimen is contrain-

Table 3 SVR Rates at 12 Weeks of Ombitasvir, Paritaprevir, Ritonavir, plus Dasabuvir, with Ribavirin, in Patients with HCV Genotype 1a without Cirrhosis

Outcome at 12 weeks of ombitasvir, paritaprevir, ritonavir, plus dasabuvir, with ribavirin	SAPPHERE-I treatment-naïve (N = 322)	SAPPHERE-II treatment-experienced (N = 173)	PEARL-IV treatment-naïve (N = 100)
SVR12, %	96	96	97
HCV indicates hepatitis C virus; SVR, sustained virologic response. Adapted from Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), copackaged, prescribing information; February 2015.			

Table 4 SVR Rates at 12 Weeks of Ombitasvir, Paritaprevir, Ritonavir, plus Dasabuvir, in Patients with Genotype 1b HCV without Cirrhosis

Outcome at 12 weeks of ombitasvir, paritaprevir, ritonavir, plus dasabuvir	PEARL-II treatment-experienced (N = 91)	PEARL-III treatment-naïve (N = 209)
SVR12, %	100	100
HCV indicates hepatitis C virus; SVR, sustained virologic response. Adapted from Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), copackaged, prescribing information; February 2015.		

Table 5 Response Rates at 12 and 24 Weeks of Treatment with Ombitasvir, Paritaprevir, Ritonavir, plus Dasabuvir, with Ribavirin, in Patients with Genotype 1 Chronic HCV with Cirrhosis

Outcome	HCV genotype 1a ombitasvir, paritaprevir, ritonavir, and dasabuvir plus ribavirin		HCV genotype 1b ombitasvir, paritaprevir, ritonavir, and dasabuvir plus ribavirin
	12 weeks	24 weeks	12 weeks
Sustained virologic response 12, % (n/N)	89 (124/140)	95 (115/121)	99 (67/68)
Sustained virologic response 12 for treatment-naïve patients, % (n/N)	92 (59/64)	95 (53/56)	100 (22/22)
Sustained virologic response 12 by previous pegylated interferon treatment			
Null responder, % (n/N)	80 (40/50)	93 (39/42)	100 (25/25)
Partial responder, % (n/N)	100 (11/11)	100 (10/10)	86 (6/7)
Relapsed, % (n/N)	93 (14/15)	100 (13/13)	100 (14/14)
HCV indicates hepatitis C virus. Adapted from Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), copackaged, prescribing information; February 2015.			

licated in patients with severe hepatic impairment.¹⁹ The combination is also contraindicated with:

- Drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events
- Drugs that are strong inducers of CYP3A and CYP2C8, which may lead to reduced efficacy of the combination of ombitasvir, paritaprevir, and ritonavir plus dasabuvir
- Drugs that are strong inhibitors of CYP2C8, which may increase dasabuvir plasma concentrations and the risk for QT prolongation.¹⁹

Warnings and Precautions

Increased risk for alanine aminotransferase (ALT) elevations. In clinical trials of ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with or without ribavirin, elevations of ALT levels to >5 times the upper limit of normal (ULN) were observed in approximately 1% of all patients.¹⁹ These ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment and declining within 2 to 8 weeks of continued dosing.¹⁹ Evaluations of hepatic function should be performed during the first 4 weeks after starting treatment, and as clinically indicated thereafter.

If elevated ALT levels are observed, close monitoring is recommended.¹⁹ Patients should consult a healthcare professional if they experience signs of liver problems, including the onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces. The discontinuation of ombitasvir, paritaprevir, and ritonavir plus dasabuvir should be considered if ALT levels remain >10 times the ULN. The 4-drug combination should be permanently discontinued if elevation in ALT levels is

accompanied by the signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio.¹⁹

Risks associated with ribavirin combination treatment. The warnings and precautions for ribavirin, including the pregnancy avoidance warning, apply when ombitasvir, paritaprevir, and ritonavir plus dasabuvir tablets are administered with ribavirin.¹⁹

Risk for HIV-1 protease inhibitor drug resistance. Ritonavir is an HIV-1 protease inhibitor. To reduce the risk for HIV-1 protease inhibitor drug resistance, patients who are HCV/HIV-1 coinfecting and who receive treatment with ombitasvir, paritaprevir, and ritonavir plus dasabuvir should also receive a suppressive antiretroviral drug regimen.¹⁹

Specific Populations

Pregnancy. Ombitasvir, paritaprevir, and ritonavir plus dasabuvir is assigned pregnancy category B; there are no adequate and well-controlled studies with this regimen in pregnant women. It should therefore only be used during pregnancy if clearly needed.¹⁹ The combination of ombitasvir, paritaprevir, and ritonavir plus dasabuvir, with ribavirin, is contraindicated in pregnant women and in men whose female partners are pregnant.¹⁹

Nursing mothers. It is not known whether the components of ombitasvir, paritaprevir, and ritonavir plus dasabuvir and its metabolites are present in human breast milk.¹⁹ The developmental and health benefits of breastfeeding, as well as the mother's clinical need for this combination and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition, should be considered.¹⁹

Pediatric use. The safety and efficacy of ombitasvir, paritaprevir, and ritonavir plus dasabuvir have not been established in pediatric patients aged <18 years.¹⁹

Geriatric use. No dosage adjustment is recommended for geriatric patients.¹⁹

Renal impairment. Patients with mild, moderate, or severe renal impairment do not require dose adjustment of ombitasvir, paritaprevir, and ritonavir plus dasabuvir.¹⁹ When managing patients with renal impairment who

Ombitasvir, paritaprevir, and ritonavir tablets plus dasabuvir tablets represents a novel, multitargeted treatment option for patients with genotype 1 HCV infection.

require combination therapy with ribavirin, the prescribing information for ribavirin should be consulted.¹⁹

Hepatic impairment. No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A). Ombitasvir, paritaprevir, and ritonavir plus dasabuvir is not recommended in patients with HCV and moderate hepatic impairment (Child-Pugh B), and is contraindicated in patients with severe hepatic impairment (Child-Pugh C).¹⁹

Conclusion

Twice-daily ombitasvir, paritaprevir, and ritonavir plus dasabuvir is a very active and safe oral option for patients with genotype 1 HCV infection. Overall, 6 phase 3 studies have demonstrated high rates of response in all patient subgroups, suggesting that this copackaged oral combination of 3 new antiviral drugs plus a CYP3A inhibitor is effective across a broad range of treatment-naïve and treatment-experienced patients with HCV genotype 1 infection. Ombitasvir, paritaprevir, and ritonavir tablets plus dasabuvir tablets represents a novel, multitargeted treatment option for patients with genotype 1 HCV infection. ■

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